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GCP Introduction / Refresher

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Objectives

- To provide a refresher on the regulations and guidelines to be followed.
- To provide information on recent changes in the regulations and guidelines.

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Agenda

- Clinical Trials Process
- ICH Intro/Refresher and Update
- EU Regulations and Guidelines
- Update on UK
- FDA Regulations
- GCP for Laboratories

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What is a Clinical Trial

'clinical trial': any investigation in **human subjects** intended to **discover or verify** the clinical, pharmacological and/or other pharmacodynamic effects of **one or more investigational medicinal product(s)**….

Clinical Trials Directive, 2001/20/EC

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The Clinical Trial Process

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The Drug Development Process

- From molecule to market place…

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Clinical Trial Phases - Poll

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Clinical Development Phases & Types of Clinical Trial

- Phase I
- Phase II
- Phase III – a and b
- Phase IV
- PASS/PAES
- Post Marketing Observational
- Epidemiology

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Clinical Trial Processes

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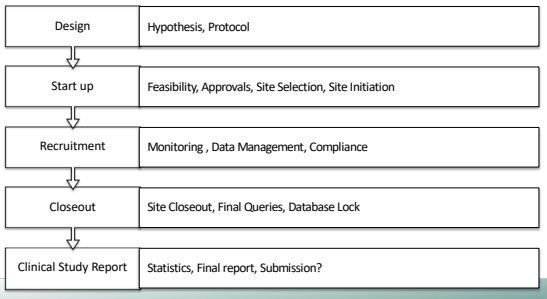
The life cycle of a clinical trial



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Approvals Required

- Regulatory Approval (CTA or IND)
- Ethics Committee Approval (HRA in the UK, IRB in the US)
- Local Approvals if required – e.g. local health service

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ICH

- International Council on Harmonisation
- US, EU and Japan
- Purpose:
  - Harmonise marketing authorisation requirements
  - Reduce timelines and cost
  - Reduce subject exposure to investigational products

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ICH Guidelines

- Q – quality topics
- S – safety topics
- E – efficacy topics
- M – multidisciplinary topics

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ICH Guidelines

- Efficacy topics
  - Many Guidelines
  - E6 is the GCP Guideline
  - E2A to E2F are all about safety data
  - E3 is Structure and Content of Clinical Study Reports

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ICH GCP

- ICH guideline E6
- No legal force
- Accepted by most countries now

Protection of human subjects

Quality of data

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ICH GCP

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1. Glossary
2. Principles

Responsibilities
3. Institutional Review Board/Independent Ethics Committee
4. Investigator
5. Sponsor

Documentation
6. Protocol / amendments
7. Investigator's Brochure
8. Essential Documents

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Who is responsible?

- Poll

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ICH E6 Addendum

- Finalised November 2016
- Increased complexity and globalisation
- Makes additions but no changes to original text

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Update to ICH E6

- Proposals to facilitate
  - Implementation of new technologies
  - Risk Management
  - Risk Based Monitoring
  - Focus on critical study elements

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Ethics Committees

- Review trial for ethics
- Appropriately constituted
- Keep records for 3 years

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Investigator

- Trial conduct at site
- Welfare of participants
- Informed Consent
- Data collection and reporting
- Management of IMP at site

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Sponsor

- Design, management and funding
- Regulatory requirements and compliance
- Risk based quality management
- Monitoring and oversight
- Safety review and reporting
- Final study report

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ICH GCP

- Ultimate responsibilities
  - Sponsor
    - Funding
    - Regulatory requirements
    - Ensuring Protocol, GCP and GMP compliance
  - Investigator
    - Trial Conduct at site
    - Subject safety and wellbeing
- Can delegate task but not responsibility
- Need very clear documentation

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ICH GCP

- Essential Documents
  - Protocol and Amendments
    - How the study is to be conducted
  - Investigator's Brochure
    - All about the investigational product
  - CRF
    - Where all the study data are recorded
  - Trial Master File/ Investigator Site File
    - All documentation and correspondence

"If it's not documented it didn't happen!"

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ICH E8 and E6 “Renovation”

- ICH consulting on revision of E8 (General Considerations) and E6
- E8 currently in draft
- E6 draft principles available
- More information on ICH website

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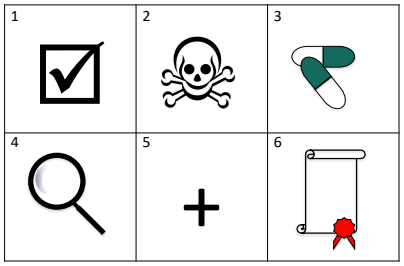
Eudralex Vol 10



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New EU Regulation

- Final version now published
- Implementation 6 months after database is finalised
- Will apply from 31 January 2022
- “will ensure that the rules for conducting clinical trials are identical throughout the EU”

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EU Regulation – Key Changes

- Authorisation
  - Fast
  - Single outcome
- Simplified reporting procedures
- Transparency on trial status and results
- EMA inspection powers

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Authorisation

- Can't use this system until database is ready (at least 2016)
- Part I
  - Assessment by Reporting Member State (RMS)
  - Coordinated review by all involved member states
  - Consolidation by RMS

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Authorisation

- Part 2
  - National review (done in parallel with part 1)
- National approval based on reports from part 1 and part 2

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UK Legislation

- **SI 2004 No.1031**
- SI 2005 No. 2754 and 2759
- **SI 2006 No.1928** and 2984
- SI 2008 No. 941
- SI 2009 No. 1164

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SI 2004 No. 1031

- Medicines for Human Use (Clinical Trials) Regulations 2004
- Contains 9 parts and 12 schedules

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1031

- **Parts:**
  1. Introductory Provisions
  2. Ethics Committees
  3. Authorisation For Clinical Trials And Ethics Committee Opinion
  4. Good Clinical Practice And The Conduct Of Clinical Trials
  5. Pharmacovigilance
  6. Manufacture And Importation Of Investigational Medicinal Products
  7. Labelling Of Investigational Medicinal Products
  8. Enforcement And Related Provisions
  9. Miscellaneous Provisions

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SI 2006 No. 1928

- The Medicines for Human Use (Clinical Trials) Amendment Regulations 2006
- Produced to implement GCP Directive
- Does not supersede 1031, but does make some amendments to it.

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1928

- Many of the sections are correcting typos, making amendments which reflect the changes in the EU or including references to the GCP Directive
- Some new provisions and changes were significant – Serious Breaches!!

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SI 2006: 1928

- Notification of Serious Breaches
  - Sponsor to notify licensing authority in writing of serious breaches of GCP or the Protocol within 7 days of becoming aware
  - Serious breach is one which is likely to significantly affect the wellbeing of subjects or the scientific value of the trial.

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Serious Breaches

- Currently UK requirement
- Will come in when CT Regulation applies
- Draft EMA guidance issued
- MHRA guidance still available

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Serious Breaches

- Examples

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Serious Breach?

- One subject was administered 6 additional doses of IMP. The subject was to receive IMP on day 1 and 8 but instead received IMP on days 1 to 8. The subject experienced a severe adverse event as a result.

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Serious Breach?

- A subject took IMP that had expired two days ago. The subject did not experience any adverse events and this issue was not likely to affect the data credibility of the trial.

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Brexit

- EU Legal representative
- If no EU office outside UK will need to appoint a legal representative to run trials in the EU

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IMP in "No-Deal Brexit"

- QP certification from other EU countries will still be recognized, but UK QP review needed – 12 months to comply
- IMPs can be sent direct to investigational sites
- Import license will be required – 12 months to comply
- Will need EU QP release to export from UK

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Brexit

- CTA process
  - Now have to use UK system rather than EU system
  - cWoW will roll out this year
- Need to register trial and results in a public database e.g. clinicaltrials.gov
- UK will have its own portal and public database in due course

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Brexit

- Expedited safety reports
  - Cannot now use Eudravigilance for reports in UK
  - Must use MHRA online system

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The Future in the UK

- MHRA consulting on revised legislation
- First new legislation likely to come out later this year
- Second phase next year
- Many aspects of EU CTR and ICH E6(R3) will be implemented

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GCP Regulations

21 CFR

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Code of Federal Regulations

- CFR Title 21
- US legislation governing food, drugs (including biologicals), cosmetics, radiation emitting devices, medical devices, veterinary products
- Parts we need to know about:
  - 11 – electronic records and electronic signatures
  - 50 – protection of human subjects (informed consent)
  - 54 – Financial Disclosure by clinical investigators
  - 56 – Institutional Review Boards
  - 201 – Labelling
  - 312 – Investigational New Drug application

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EU vs US

US	EU
	CTA
	IEC
1572	
Financial Disclosure	

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GCP for Clinical Laboratories

Issues to consider

- Logistics
  - Transport
  - Receipt
  - Identification
  - Storage

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Issues to consider

- Processing
  - Method Validation
  - Standards
  - Data
  - Repeat analysis
  - Blinding/Unblinding

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GCP for Clinical Laboratories

Issues to consider

- Facilities and equipment
- QA and QC

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Data Handling

"It was not possible to verify that the laboratory method used was the one that had been validated as the scientist who had performed the research had left the laboratory, taking the method development and validation records with him."

MHRA inspection finding

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GCP for Clinical Laboratories

The Patients

- Safety
  - Adverse Event reporting
  - Eligibility and enrollment decisions
  - Other issues which might impact subject safety
- Consent
  - Only perform tests in the protocol and consent form
  - Withdrawal of consent
  - Death of a patient
- Confidentiality
  - Patient identification
  - Labelling and forms

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GCP for Clinical Laboratories

Exercise

- For each of the following outline how you could demonstrate to an inspector that you have met GCP requirements
  - Patients have consented to the tests being performed
  - Only tests required by the clinical trial protocol are performed on samples in the lab
  - Source data can be used to verify information in the laboratory reports
  - There is a system in place for alerting results that are unexpected and/or significant deviations from pre- specified limits

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Summary

- Clinical Trials Process
- ICH Intro/Refresher and Update
- EU Regulations and Guidelines
- Update on UK
- FDA Regulations
- GCLP

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Thank you for coming!

- Feedback forms
- Certificates
- Follow up information

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